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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/334,325	06/16/1999	STEWART A. CEDERHOLM-WILLIAMS	CV0276A	5209

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1633	15

DATE MAILED: 12/19/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/334,325	Applicant(s) CEDERHOLM-WILLIAMS, STEWART A.	
	Examiner Shin-Lin Chen	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 13-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

1. The request filed on 10-16-01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/334,325 is acceptable and a CPA has been established. An action on the CPA follows.

The preliminary amendment filed 10-16-01 has been entered. Claims 3 and 4 have been canceled. Claims 1, 2 and 13-16 are pending and under consideration.

Priority

2. If applicant desires priority under 35 U.S.C. 119 (e) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The benefit of provisional application 60/083,571, filed 4-30-98, has been claimed in Oath/Declaration but the claimed priority has not been mentioned at the first sentence of the specification following the title.

Further, the benefit of nonprovisional application 09/303,377, filed 4-30-99, has been claimed in Oath/Declaration. An application in which the benefits of an earlier application, 09/303,377, are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78). Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 2 and 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of transforming a cell *in vitro* by applying a nucleic acid and a pliable, adhesive fibrin gel to said cell, does not reasonably provide enablement for a method of transforming a cell *in vivo* by applying a nucleic acid and a pliable, adhesive fibrin gel to said cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1, 2 and 13-16 are directed to a method of transforming cells by applying nucleic acid, such as a plasmid or the nucleic acid is incorporated in a virus, and fibrin gel to the cells separately, or applying nucleic acid in admixture with fibrin or fibrinogen composition to the cells. The claims read on combining a fibrin gel with any vector or virus carrying the nucleic acid to transform cells *in vivo* at any location of any subject including human beings, mammals, fishes, birds, insects, fungus, plants etc.

The specification discloses the preparation of preferred sealant compositions and the incorporation of nucleic acid into fibrin gel, but fails to provide an enabling disclosure for the method of using fibrin monomer or fibrinogen that forms fibrin gel for genetic transformation of

any nucleic acid or virus containing said nucleic acid at any location of a subject *in vivo*. The specification fails to provide adequate guidance and evidence for transforming cells *in vivo* via the combination of a nucleic acid, a vector or a virus with a fibrinogen composition or a fibrin gel. No teachings are present within the specification in regard to how to transform cells with any nucleic acid in any vector or any virus containing said nucleic acid by using fibrinogen composition or fibrin gel, how the nucleic acid entrapped in fibrin gel can be taken up by cells, and whether the nucleic acid taken up by cells can be expressed in said cells *in vivo*.

Marshal (Science, 1995, Vol. 269, p. 1052-1053) states that adenovirus genes express proteins that trigger immune responses and provoke inflammation along with an immune attack that neutralizes cells containing adenovirus genes (e.g. p. 1052, right column). Nabel et al., 1994 (Annals New York Academy of Science, Vol. 714, p. 247-252) indicates several issues relevant to the application of adenoviral vectors to human therapies need to be investigated, including stability of gene expression and host-cell immune response (e.g. bridging page 248, 249). Verma et al., 1997 (Nature, Vol. 389, p. 239-242) points out that the use of virus vectors for gene delivery has been confronted by the host immune responses (e.g. p. 239, right column). Further, it was known in the art that DNA or nucleic acid itself could stimulate host immune responses to said DNA or nucleic acid. In view of such, it is unclear whether the combination of a fibrin composition or a fibrin gel with a nucleic acid or a virus containing said nucleic acid can transform cells *in vivo* such that said nucleic acid is expressed in said cells. Therefore, it would have required one skilled in the art at the time of the invention undue experimentation to practice

over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 2 and 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Donovan, 1998 (US patent No. 5,833,651).

Claims 1, 2 and 13-16 are directed to a method of transforming cells by applying nucleic acid, such as a plasmid or the nucleic acid is incorporated in a virus, and fibrin gel to the cells separately, or applying nucleic acid in admixture with fibrin or fibrinogen composition to the cells. The claims read on combining a fibrin gel with any vector or virus carrying the nucleic acid to transform cells *in vivo* at any location of any subject including human beings, mammals, fishes, birds, insects, fungus, plants etc.

Donovan teaches a method for delivering nucleic acid to cells accessible from a wall of a body lumen comprising providing a stent having a lumen-wall contacting surface, a lumen-

exposed surface, a first polymer composition comprising fibrin covering at least a portion of the lumen-wall contacting surface to form a polymer covered stent, and a virus to deliver nucleic acid to a cell wherein the virus is associated with the first polymer composition covering the lumen-wall contacting surface, and positioning said stent in a lumen of the body to deliver said nucleic acid to said cell. Donovan also teaches using a second polymer composition comprising fibrin to cover at least a portion of the first polymer composition on the lumen-wall contacting or lumen-exposed surface of the stent (e.g. column 3, 4, 20). Donovan constructed plasmid pCMVhpAP expressing the reporter hpAP gene under the control of CMV promoter and an E1 deleted recombinant adenoviral vector ADVhpAP expressing hpAP, and prepared a fibrin covered stent which was placed in a solution of plasmid or virus overnight to load the plasmid or virus into the fibrin covered stent for determining whether fibrin enhances gene delivery to the artery (e.g. column 18, 19, 20). However, Donovan does not provide evidence for a successful cell transformation *in vivo* via the method set forth above such that a nucleic acid is expressed in the transformed cells. Donovan further teaches mixing a solution of fibrin monomer and virus containing nucleic acid to form a polymer, i.e. fibrin gel, which can be used to deliver the virus to the cell (e.g. column 13). Donovan does not specifically teaches applying a nucleic acid to cells first then adhering a pliable, adhesive fibrin to the cells.

It would have been obvious for one of ordinary skill at the time of the invention to apply a nucleic acid to cells first then adhering a pliable, adhesive fibrin to said cells to entrap said nucleic acid because adding a nucleic acid to cells before, during, or after the formation of a

pliable, adhesive fibrin gel are for the same purpose of entrapping the nucleic acid in fibrin gel to deliver said nucleic acid to said cells and would be obvious for one of ordinary skill. Further, mixing a solution of fibrin monomer and virus containing nucleic acid would form a pliable and adhesive fibrin gel before the gel become not pliable. Thus, it would have been obvious for one of ordinary skill at the time of the invention to use a pliable, adhesive fibrin gel to entrap a nucleic acid or a virus containing said nucleic acid.

One having ordinary skill at the time the invention was made would have been motivated to apply a nucleic acid to cells before, during, or after the formation of a pliable, adhesive fibrin gel in order to entrap the nucleic acid in fibrin gel and deliver said nucleic acid to said cells *in vitro* such that said nucleic acid is expressed in said cells with reasonable expectation of success according to the teachings of Donovan.

It should be noted that although Donovan suggests using heparin to prevent or limit thrombosis, adding heparin is just an alternative for the method taught by Donovan. Donovan suggests adding heparin after fibrin polymerization has been largely completed and the ratio of heparin to fibrinogen does not damage the integrity of the fibrin structure or lead to a weak fibrin covering (e.g. column 8, 9). As discussed above, the teachings of Donovan would render the claimed method of the present application obvious for one of ordinary skill at the time of the invention. Thus, claims 1, 2 and 13-16 are rejected under 35 U.S.C. 103(a).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Kimberly Davis, whose telephone number is (703) 305-3015.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.